CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-547

CORRESPONDENCE

BEDFORD
LABORATORIES™

March 1, 2001

Response to Telephone Amendment/
Chemistry Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

[redacted]
N/Am

RE: **ANDA 75-547**
Product: **Thiotepa for Injection USP - 15 mg per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application 75-547, Thiotepa for Injection USP, 15 mg/vial, by revising the Active Drug Substance Specifications for Bioload test. This is in reference to the telephone conversation of March 1, 2001, between Ms. Pratima Patel of Ben Venue Laboratories and Mr. Mike Smela of the Agency.

FDA form 356h is provided.

Attached, please find revised Active Drug Substance Specifications for Thiotepa, USP. Per the Agency's request, the Bioload Specifications have been revised as follows:

Bioload	Response Level 1	Current USP

We trust this meets your approval. However, if the Agency needs any assistance in the review of this application, the phone numbers for contact are (440) 201-3333 (direct) and (440) 232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel fax

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

February 26, 2001

Response to Telephone Amendment/
Chemistry Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

RE: **ANDA 75-547**
Product: **Thiotepa for Injection USP - 15 mg per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application 75-547, Thiotepa for Injection USP, 15 mg/vial, by revising the Finished Product Release Specifications and Drug Product Stability Specifications. Also, we have revised our expiry period to 12-months from 24-months. This is in reference to the telephone conversation of February 22, 2001, between Ms. Pratima Patel of Ben Venue Laboratories and Mr. Mike Smela and Mr. Ken Furnkranz of the Agency.

FDA form 356h is provided.

Revised Finished Product Specifications and Drug Product Specifications are provided in this amendment. The Finished Product Specifications (Section XV of the original Application) will be used to release the finished dosage form, where as the Drug Product Specifications (Section XVI of the original Application) are Stability Specifications.

Also, per the Agency's request, we have revised our expiry period from 24-months to 12-months; the Post-Approval Stability Protocol has been revised to reflect this change by deleting the 18- and 24-months test points. The Specifications for Chromatographic Purity have been updated based on available stability data.

Bedford Laboratories™ commits to filing a Prior-Approval Supplement to extend the approved expiration date of 12-months and requests the Agency's guidance in this matter, as Bedford Laboratories™ has previously provided 24-months shelf-life data in support of our proposed 24-months expiry.

We trust this meets your approval. However, if the Agency needs any assistance in the review of this application, the phone numbers for contact are (440) 201-3333 (direct) and (440) 232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

P. Patel for

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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ORIG AMENDMENT

N/AM

February 2, 2001

Response to Minor Amendment
Chemistry and Microbiology Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-547**
Product: **Thiotepa for Injection USP - 15 mg per vials**

Dear Sir:

We wish to amend our unapproved abbreviated new drug application 75-547, Thiotepa for Injection USP, 15 mg per vials by responding to the Agency's letter dated April 21, 2000.

FDA form 356h is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. The Drug Substance manufacturer has responded to their DMF deficiency letter on January 31, 2001. A copy of the correspondence letter from , agent. .s provided in Attachment II.

2. The tests and specifications sheet has been updated by including all the tests from current USP. The test method # for Residual Solvents has been updated. Please refer to Attachment III for revised tests and specifications sheet for Thiotepa, USP.

3. The Assay results will be reported as a single determination, not as a "mean". Please refer to Attachment III for revised Finished Product and Drug Product Stability Specifications.

4.

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Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

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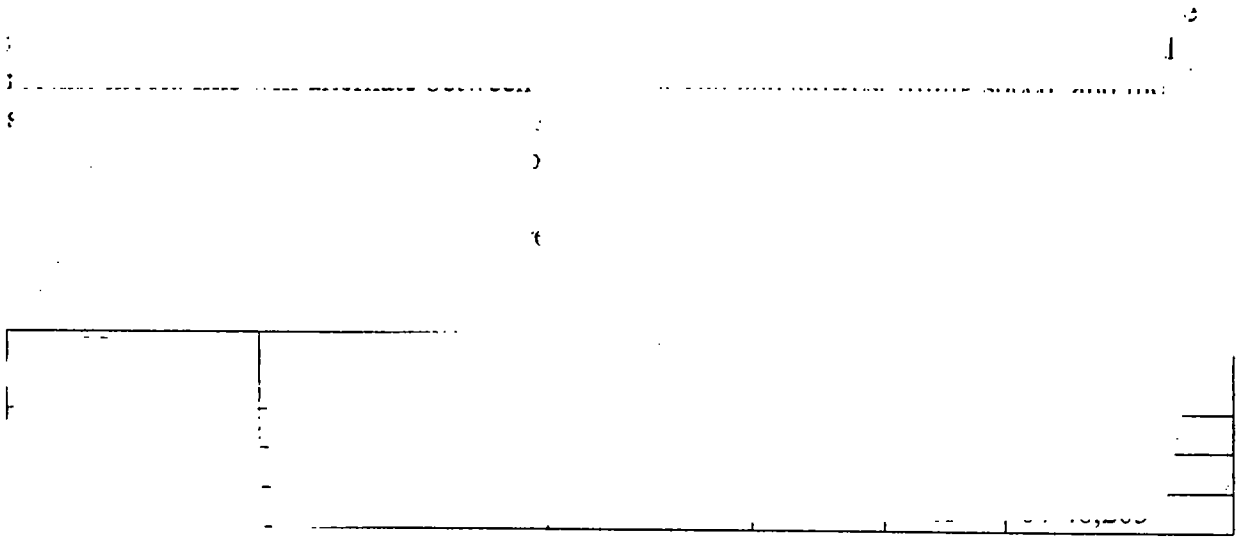
process.

2.



3. If we extend the expiration date to 30-months in the future, Bacterial Endotoxins test will be conducted at 30-month test point.

In addition to, we acknowledge that a satisfactory cGMP compliance evaluation for the firms referenced in this application is required.

We trust this meets your approval. However, if the Agency needs any assistance in the review of this application, the phone numbers for contact are (440) 201-3333 (direct) and (440) 232-2772 (Fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

[APR 21 2000]

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-547 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Thiotepa for Injection, 15 mg/vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

4/21/01

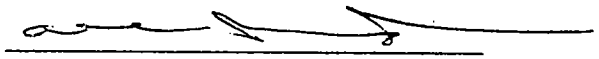
. The RLD
and tested

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The microbiologist's review of the submission for sterility assurance is pending.

2. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation & Research

BEDFORD
LABORATORIES™

March 22, 2000

Response to Minor Amendment
Chemistry and Labeling Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

FDA DRUG AMENDMENT

RE: **ANDA 75-547**
Product: **Thiotepa for Injection USP - 15 mg per vials**

Dear Sir:

We wish to amend our unapproved abbreviated new drug application 75-547, Thiotepa for Injection USP, 15 mg per vials by responding the Agency's letter dated February 17, 2000.

FDA form 356h is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. We have contacted the DMF holder. The Drug Substance manufacturer has responded to their deficiency letter on March 14, 2000. A copy of the correspondence letter from ' US agent, and a letter indicating that i: authorized agent are provided in Attachment II.

2. We acknowledge your comment. Bedford Laboratories will formulate all commercial batches with f active drug substance, to be consistent with the innovator formulation. To reflect this change, revised Compounding Instructions along with master manufacturing records are provided in Attachment III. Please note that this change has been reflected in the package insert labeling, which is provided in Attachment VI.

3. The specifications for ıould be no more than he revised test specifications for the active drug substance is provided in Amendment IV.

4. For all future incoming lots of Thiotepa, USP, Bedford Laboratories commits to calculate and report the drug substance assay results on the ıasis.

5. We acknowledge your comment. Residual solvents testing will be performed on all future lots of Thiotepa, USP; therefore, we would like to omit the residual solvents test for finished product. The revised finished product specifications are provided in the Attachment IV.

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6. Finished product specifications are revised to include the identification test. Please refer to Attachment IV for revised finished product specifications.

7. In the assay test method sample preparation for the assay has been revised to include a composite sample of individual vials (refer to page 4 of 19, sample preparation for assay method). Revised test method is provided in Attachment V.

8. We acknowledge your comment. The 18-months label temperature stability data is provided in Attachment IV for your review. Moreover, the 24-months stability data will be provided as soon as it is available to request 24-months expiry period for this product.

B. In addition to, we acknowledge following:

1. The microbiologist's review of the submission for sterility assurance is pending.

2. Response to the labeling deficiencies is included in this amendment.

3. A satisfactory cGMP compliance evaluation for the firms referenced in this application is required.

4. As we commented in the response # 8, 24-months stability data will be provided to request 24-months expiration period for the product.

Labeling Deficiencies:

We have updated our package insert labeling based on your comments. Twelve copies of final printed package insert labeling are provided in Attachment VI for your review. Also, annotated side-by-side comparison of our proposed labeling with our last submission, with all differences highlighted, is provided in this attachment.

We trust this meets your approval. However, if the Agency needs any assistance in the review of this application, the phone numbers for contact are (440) 232-3320, ext. 333 (direct) and (440) 232-2772 (Fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

July 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/Ac

RE: **ANDA 75-547/Major Amendment**
Product: **Thiotepa for Injection USP - 15 mg per vials**

Dear Sir:

We wish to amend our unapproved abbreviated new drug application 75-547, Thiotepa for Injection USP, 15 mg per vials by responding the Agency's letter dated June 17, 1999.

FDA form 356h is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

1. The reference listed drug contains 15.6 mg/vial of drug product (refer to approved reference listed drug's package insert). To be identical to the reference listed drug, the proposed drug product was formulated at Based on the label temperature and accelerated temperature stability data, the proposed drug product does not require The manufacturing instructions have been updated, which do not contain . Please refer to Attachment II for updated manufacturing records.

2. We have contacted the DMF holder. The Drug Substance manufacturer has responded to their deficiency letter on July 8, 1999. A copy of the correspondence letter from DMF holder is provided in Attachment III.

3. The active drug substance specifications are updated to include Bacterial Endotoxins test with NMT specifications. Bioload test (Microbial limit test) has been included in the original application, which confirms the absence of *Staphylococus aureus, Pseudomonas aeruginosa, salmonella* and *E. Coli.* Please refer to Attachment IV for preparatory testing for bioload testing of the active drug substance thiotepa, USP.

4. Please refer to Attachment V for updated finished product release and drug product specification for pH. The pH specification has been revised to "between from

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JUL 22 1999
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5.

6. Please refer to Attachment V for revised Post Approval Stability Commitment (page 613 of original application), which has an inclusion of control room temperature range of +2° C to +8°C.

7. The reference listed drug product has 9 month expiry period; therefore, the stability samples of exhibit batch were scheduled to test an additional test point of one month before and after (8 and 10 month) the RLD's expiry date. Ben Venue has requested 24-month expiration date based on the three months accelerated temperature stability data. Additionally, per the Agency's stability guideline, testing is required every three months during the first year and 6 months during the second year. Therefore, testing at 8 months is not required for the proposed drug product. Please refer to Attachment V for updated post-approval stability protocol, where 8-months test point has been deleted.

8. The stability samples will be stored in the upright position. If the drug product stored in an inverted or on the side position, the drug product will come in contact with closure system, but the likely hood of any chemical reaction between the and the closure is very unlikely.

9. Please refer to Attachment VI for the pH studies, which were conducted using Sterile Water for Injection, USP. The stability samples were placed under accelerated temperature for three months and tested for pH. Since the proposed drug product meets the pH specifications listed in the USP XXIII, Supplement 10, Bedford Laboratories will label the product as Thiotepa for Injection, USP. This change has been reflected in our revised master batch records, label and labeling.

10. Please refer to Attachment VII for the updated Environmental Impact Analysis Report.

B. In addition to, we acknowledge that the microbiologist's review of the submission for sterility assurance is pending.

We have updated our vial label, carton and package insert labeling based on your comments. Twelve copies of final printed label and labeling are provided in Attachment VII for your review. Also, annotated side-by-side comparison of our proposed labeling with our last submission, with all differences highlighted, is provided in this attachment.

We trust this meets your approval. However, if the Agency needs any assistance in the review of this application, the phone numbers for contact are (440) 232V-3320, ext. 333 (direct) and (440) 232-2772 (Fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

JUN 17 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-547 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Thiotepa for Injection, 15 mg/vial

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please justify formulating at Label Claim.

2. Drug Master File for the active ingredient is deficient. The Drug Master File Holder has been notified.

3. Please revise the specifications for the active ingredient to include testing for Bacterial Endotoxins EU/mg) and Microbial Limit - the absence of Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella and E. Coli.

4. The proposed drug product release specification for pH is ... Please revise this specification to "between 5".

5. Release data for Residual Solvents for test lot 69881 are "none detected" for and Please justify the proposed specifications for

6. Per the post approval stability protocol, samples of the product will be tested at CRT of +2° C + 8° C at 0, 3, 6, 9, 12, 18, 24 and 30-months (page 613). The statement should be revised to include the storage temperature of the drug product. The statement should read "Samples of the product will be stored and tested at CRT of +2° C + 8° C ...".

7. Per the post approval stability protocol, the test stations per the schedule on page 611 also include an 8-month test station. The test stations should be clarified.

8. Per the post stability protocol, the storage position of the containers is not described. Please store containers of each lot in both the upright and the inverted or on the side positions. Stability samples stored in an inverted or on the side position should be tested at all scheduled test stations, and samples stored upright should be tested

at less frequent but regular intervals until adequate comparative data are available. Upright samples should be maintained as controls so that they are available if needed. These studies of the drug product are necessary to determine if product integrity or stability is affected due to leaching of chemicals from the closure components.

9. The stability studies do not support the proposed specification for pH.

   We acknowledge your statement that the studies are being repeated wherein the samples were reconstituted with Sterile Water for Injection, and the results will be submitted to the ANDA as an amendment as soon as the data are available.

   Satisfactory data are required prior to approval of the application.

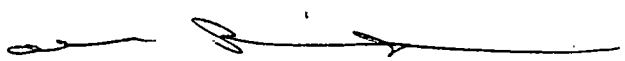
10. The request for a Categorical Exclusion for Environmental Impact Considerations referenced is CFR 25.24(C)(1). The reference should be updated per 21 CFR revised April 1, 1998 to 25.31(a).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The microbiologist's review of the submission for sterility assurance is pending.

2. Your response must also address the labeling deficiencies.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD LABORATORIES™

December 29, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

505(j)(2)(A) OK
2/8/99
Gregory D. Davis

RE: Abbreviated New Drug Application
Product: Thiotepa for Injection; 15 mg per vial

Dear Sir/Madam:

In accordance with Section 505 (j)(1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories™ is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Thiotepa for Injection, 15 mg per vial. Please note that the field copy is being sent directly to FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 300 Northfield Road, Bedford, Ohio 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Immunex's Thioplex®).

In accordance with Title 21 CFR 320.22 Bedford Laboratories™ requests a waiver of the requirements for submission of evidence demonstrating the *in vivo* bioavailability/ bioequivalence for the drug product that is the subject of our application (Thiotepa for Injection, 15 mg per vial). The drug product is intended for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug product.

Bedford Laboratories™ certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with the cGMP in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Three copies of the analytical method which was used to test this product and an analytical method validation package are enclosed separately along with this application.

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300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

Office of Generic Drugs
December 29, 1998

Thiotepa for Inj.
ANDA

The proposed drug product is being claimed as non-USP. The reason for the non compendial nature of the proposed drug product is a difference in pH of the reconstituted solution in comparison to the compendial monograph. Upon reconstitution with Water for Injection, the reference listed drug and the proposed drug product pH were found to be 6.7 and 6.8 respectively. However, the pH range listed in the USP XXIII is 7.0 to 8.6; hence, the currently marketed drug product as well as the proposed drug product do not meet the compendial specifications for pH. Furthermore, Bedford Laboratories acknowledges that the subject product is an official article in the United States Pharmacopeia (USP), and in the event of a dispute, only the results obtained by the official methods and procedures mentioned in the USP XXIII will be considered conclusive.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol and the package insert is enclosed separately with this application. This drug product was lyophilized.

If the Agency needs any assistance in the review of this application, the phone numbers for contact are (440)-232-3320, ext.333 (direct) and (440)-232-3320 (fax).

Sincerely,

for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.